## REMARKS

By the present communication, claims 63, 71, 75, 79, 81, 89, 90, 94, and 102 have been cancelled herein without disclaimer and without prejudice. Claims 66, 67, 68, 74, 78, 80, 84, 85, 86, 93, 97-99, 105-107, 122-125, and 129-145 have been amended herein. No new matter is added with the claim amendments since the amendments rewrite claims 139-145 in independent form, change dependencies of dependent claims, or correct typographical errors. Additionally, claims 133 to 138 are amended herein to recite properties of control cells that are the properties of cells recited in claims 139 to 145. The Examiner's indication that claims 139-145 would be allowable if rewritten in independent form is acknowledged with appreciation. Upon entry of this amendment, claims 66-70, 74, 78, 80, 84-88, 90, 93, 97-101, and 105-145 are pending.

### A. Rejection Under 35 U.S.C. § 112, first paragraph (enablement)

The Office Action rejects claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 under 35 U.S.C.§ 112, first paragraph, as allegedly lacking an enabling disclosure. The rejection is rendered moot by the cancellation of claims 63, 71, 75, 79, 81, 89, 90, 94, and 102, and by the change in dependency of the remaining rejected claims to a dependency from claims 139-145, which the Office Action acknowledged are allowable in independent form. Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Regarding the assertion in the Office Action that a deposit of the stable COS-7 cell line is required to meet the enablement rejection, Applicants respectfully assert that the enablement requirement is met for the pending claims without additional cell line deposits. Applicants note that this rejection was apparently not directed at pending claims 139-145, from which the remaining pending claims depend. Applicants also assert that it is not clear from the Office Action whether the assertion is directed to a deposit of COS-7 cells, or of the specific COS-7 derived cell lines disclosed in the application. Applicants note that COS-7 cells are commercially available from the American Type Culture Collection (ATCC) (See Exhibit B). A skilled artisan could transfect the commercially available COS-7 cells with

one or more vectors that include the recited elements of independent claims 139-145, to obtain cell lines with the recited characteristics, as disclosed for example, in Example 4 of the pending application. Therefore, Applicants assert that the enablement requirement is met and respectfully request withdrawal of the rejection of claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 under 35 U.S.C. § 112 first paragraph.

**B. Rejection Under 35 U.S.C. § 112, second paragraph**

The Office Action rejects claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 under 35 U.S.C.§ 112, second paragraph, as allegedly being incomplete for omitting essential elements. The rejection is rendered moot by the cancellation of claims 63, 71, 75, 79, 81, 89, 90, 94, and 102, and by the change in dependency of the remaining rejected claims to a dependency from claims 139-145, which the Office Action acknowledges are allowable in independent form. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 under 35 U.S.C. § 112, second paragraph.

In view of the above amendments and remarks, it is submitted that the pending claims are in condition for allowance, and a notice to that effect is respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: February 24, 2003

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**CUSTOMER NO. 28213**

# EXHIBIT A

## MARKED-UP COPY OF THE CLAIMS SHOWING THE AMENDMENTS

**In the Claims**

Please cancel claims 63, 71, 75, 79, 81, 89, 90, 94, and 102, without prejudice.

Please amend the claims as follows:

66. (Amended) The method of claim [63] 139, wherein said GPCR is a taste receptor.

67. (Twice Amended) The method of claim [63] 139, wherein said reporter gene is selected from the group consisting of luciferase, GFP, [chloramphenical] chloramphenicol acetyl transferase, β-galactosidase, β-lactamase and secreted alkaline phosphatase.

68. (Amended) The method of claim [63] 139, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

74. (Amended) The method of claim [71] 140, wherein said signal transduction detection system comprises an intracellular calcium indicator.

78. (Amended) The method of claim [75] 141, wherein said signal transduction detection system comprises an intracellular calcium indicator.

80. (Amended) The method of claim [75] 141, wherein said detecting comprises [flurescence] fluorescence detection.

84. (Amended) The method of claim [81] 142, wherein said detecting comprises fluorescence detection.

85. (Amended) The method of claim [81] 142, wherein said reporter gene is selected from the group consisting of luciferase, GFP, [chloramphenical] chloramphenicol acetyl transferase, β-galactosidase, β-lactamase and secreted alkaline phosphatase.

86. (Amended) The method of claim [81] 142, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

93. (Amended) The method of claim [90] 143, wherein said signal transduction detection system comprises an intracellular calcium indicator.

97. (Amended) The method of claim [94] 144, wherein said detecting comprises fluorescence detection.

98. (Twice amended) The method of claim [94] 144, wherein said reporter gene is selected from the group consisting of luciferase, GFP, [chloramphenical] chloramphenicol acetyl transferase, β-galactosidase, β-lactamase and secreted alkaline phosphatase.

99. (Amended) The method of claim [94] 144, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

105. (Amended) The method of claim [102] 145, wherein said detecting comprises fluorescence detection.

106. (Twice amended) The method of claim [102] 145, wherein said reporter gene is selected from the group consisting of luciferase, GFP, [chloramphenical] chloramphenicol acetyl transferase, β-galactosidase, β-lactamase and secreted alkaline phosphatase.

107. (Amended) The method of claim [102] 145, further comprising contacting said cells with a compound that increases calcium levels inside said cells.

122. (Twice amended) The method of claim [75] 141, wherein said GPCR is selected from the group consisting of muscarinic receptors, [nictonic] nicotinic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

123. (Twice amended) The method of claim [81] 142, wherein said GPCR is selected from the group consisting of muscarinic receptors, [nictonic] nicotinic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors

124. (Amended) The method of claim [90] 143, wherein said GPCR is selected from the group consisting of muscarinic receptors, [nictonic] nicotinic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

125. (Amended) The method of claim [94] 144, wherein said GPCR is selected from the group consisting of muscarinic receptors, [nictonic] nicotinic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

129. (Amended) The method of claim [63] 139, wherein said second heterologous promoter is NFAT.

130. (Amended) The method of claim [81] 142, wherein said second heterologous promoter is NFAT.

131. (Amended) The method of claim [94] 144, wherein said second heterologous promoter is NFAT.

132. (Amended) The method of claim [102] 145, wherein said second heterologous promoter is NFAT.

133. (Twice amended) The method of claim [63] 139, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a control cell line lacking said GPCR detected under the same conditions as in step (iii), wherein the control cell line is a COS-7 cell line comprising polynucleotides according to a and b, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

134. (Twice amended) The method of claim [71] 140, wherein said method further comprises comparing said change in signal detected in step (iii) with a change in signal detected in a control cell line lacking said GPCR detected under the same conditions as in step (iii) , wherein the control cell line is a COS-7 cell line comprising polynucleotides according to a, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

135. (Twice amended) The method of claim [75] 141, wherein said method further comprises comparing said change in signal detected in step (ii) with a change in signal detected in a control cell line lacking said GPCR detected under the same conditions as in step (ii), wherein the control cell line is a COS-7 cell line comprising polynucleotides according to a, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

136. (Twice amended) The method of claim [81] 142, wherein said method further comprises comparing said change in reporter gene expression detected in step (ii) with a change in reporter gene expression detected in a control cell line lacking said GPCR detected under the same conditions as in step (ii), wherein the control cell line is a COS-7 cell line comprising polynucleotides according to a and b, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

137. (Twice Amended) The method of claim [90] 143, wherein said method further comprises comparing said change in reporter gene expression detected in step [c)] (iii) with a change in signal detected in a control cell line lacking said GPCR wherein said change is detected under the same conditions as in steps [b) and c)] (ii) and (iii), wherein the control cell line is a COS-7 cell line comprising polynucleotides according to a, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

138. (Twice amended) The method of claim [94] 144, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a control cell line lacking said GPCR, detected under the same conditions as in step (ii) and (iii), wherein the control cell line is a COS-7 cell line comprising polynucleotides according to a and b, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

139. (Amended) [The method of claim 63] A method of identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising:

(i) providing a cell, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction,

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell,

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with said ligand; and

(iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand, wherein the cell is a COS-7 cell comprising polynucleotides according to a, b, and c, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further

comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

140. (Amended) [The method of claim 71] A method for identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising:

(i) providing a cell, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2, and

b) a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction, and

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein, and

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein,

wherein said GPCR is not naturally expressed in said cell, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with said ligand; and

(iii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said ligand with said signal after addition of said ligand, wherein said signal transduction detection system comprises a

dye, wherein the cell is a COS-7 cell comprising polynucleotides according to a and b, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

141. (Amended) [The method of claim 75] A method of a identifying a ligand for a G-protein coupled receptor (GPCR), the method comprising:

(i) contacting a cell with a test chemical, said cell comprising

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2, and

b) a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction,

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein,

wherein said GPCR is not naturally expressed in said cell, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and

(ii) detecting a change in a signal with a signal transduction detection system

by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical, wherein said signal transduction detection system comprises a dye, wherein a change in reporter gene expression identifies the test compound as a ligand for the GPCR, thereby identifying the ligand for the GPCR, wherein the cell is a COS-7 cell comprising polynucleotides according to a and b, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

142. (Amended) [The method of claim 81] A method of identifying a ligand for a G-protein coupled receptor (GPCR), the method comprising

(i) contacting a cell with a test chemical, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction, and

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein, and

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and

(ii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said test chemical with reporter gene expression after addition of said test chemical, wherein a change in reporter gene expression identifies the test compound as a ligand for the GPCR, thereby identifying the ligand for the GPCR, wherein the cell is a COS-7 cell comprising polynucleotides according to a, b, and c, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

143. (Amended) [The method of claim 90] A method for identifying a modulator of signal transduction mediated by G-protein coupled receptor (GPCR) activation in a cell, the method comprising:

(i) contacting a cell with a ligand that in the absence of a test chemical, activates signal transduction in said cell, said cell comprising

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2, and

b) a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction, and

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein, and

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein,

wherein said GPCR is not naturally expressed in said cell, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with the test compound, and

(iii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical, wherein the cell is a COS-7 cell comprising polynucleotides according to a and b, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

144. (Amended) [The method of claim 94] A method for identifying a modulator of signal transduction in a cell, the method comprising:

(i) contacting a cell with a ligand that in the absence of a test chemical, activates signal transduction via a GPCR in said cell, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction,

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell,

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with the test compound; and

(iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said test chemical with reporter gene expression after addition of said test chemical, wherein the cell is a COS-7 cell comprising polynucleotides according to a, b, and c, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further

comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

145. (Amended) [The method of claim 102] A method of functionally profiling a test chemical, comprising the steps of:

(i) contacting a panel of cells with a test chemical, said panel of cells comprising a plurality of cell clones, each cell clone comprising

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction,

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is sufficient to permit promiscuous coupling to said GPCR,

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein,

wherein said GPCR is not naturally expressed in said cell,

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and

wherein each cell clone differs only with respect to said GPCR that is expressed;

(ii) contacting said cell clones with a test chemical;

(iii) detecting reporter gene expression from said cell clones; and

(iv) comparing reporter gene expression between said cell clones, wherein the cell is a COS-7 cell comprising polynucleotides according to a, b, and c, wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further comprise a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

**EXHIBIT B**

**AMERICAN TYPE CULTURE COLLECTION COS-7 CELL LINE PRODUCT DESCRIPTION**